IRB
A Bimonthly Review of Human Subjects Research

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Volume 9 Number 3 May/June 1987

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Determining Risk to Subjects: Exposure to Ultrasound

by Wesley L. Nyborg

Ultrasound is used widely for medical applications, and continued research in this area is much needed in order to define, improve, or extend the applications. While important investigations can be carried out by using small animals or other systems as experimental models, the final evaluation of clinical techniques must be done with humans subjects. This article will provide some information which, it is hoped, will be helpful to members of Institutional Review Boards (IRBs) in reviewing proposals for research in which human volunteers receive exposure to ultrasound.

Ultrasound and its Medical Applications

Ultrasound is a form of sound; that is, it is a mechanical disturbance that passes through air, water, human tissue, or other media, causing temporal variations of pressure as it does so. In a continuous-wave sound field the pressure at any point rises and falls cyclically many times per second at a regular rate (the frequency), measured in hertz (Hz). Sound is audible to the average human ear if its frequency lies between about 20 Hz and 20,000 Hz. The sound is considered to be *ultrasound* if its frequency is above the audible limit. In medical applications of ultrasound the frequency typically lies between one and ten million hertz, i.e., between 1 MHz and 10 MHz. (See Table 1 on page 2.)

Ultrasound is used medically for both therapeutic and diagnostic purposes. For decades, physical therapists have employed ultrasound to stimulate repair of soft-tissue injuries and to relieve pain. Heat is generated as ultrasound passes through tissue, and is thought to be largely responsible for its effectiveness in therapy. Heating is sought deliberately in recent applications, where ultrasound beams are directed toward specific regions of the body, in carefully controlled patterns, in order to treat tumors with hyperthermia. Nonthermal features of the ultrasound (discussed later) are also responsible for biological effects involved in some applications.

While its use in physical therapy first made ultrasound a part of clinical practice, it is through diagnostic applications that ultrasound has now become a major medical technique. As a measure of the phenomenal growth in the latter applications, sales of ultrasonic scanners are estimated to have increased from $17 million in 1974 to $270 million in 1981. One of the dominant classes of applications is in obstetrics, where ultrasound is used to examine the embryo and fetus at all stages of gestation. Another important class of applications is in cardiology, where ultrasound is used as a real-time tool to study the structure and functioning of the heart and circulatory system. Ultrasound has been employed diagnostically for virtually every region of the body, and new applications are continually being developed.

A primary technique for diagnosis, the pulse-echo technique, depends on the transmission of short pulses of ultrasound into a patient's body and the reception of echoes reflected from various anatomical structures. With modern instruments the pulses are focused, steered, and scanned over regions of interest. Information from the echoes received is displayed on a screen to give an instantaneous view of structures in the body.

A second technique depends on the Doppler effect. An ultrasound beam is transmitted into the body and is reflected from moving objects, such as valves of the heart, or red cells flowing with the blood in an artery or vein. The reflected sound differs in frequency from the original by an amount proportional to the velocity of the object from which it is reflected. Instruments for Doppler studies provide information on velocities, presented in a variety of ways. Techniques that combine Doppler and pulse-echo methods are presently used for studying blood flow in various parts of the adult or fetal body.

Biological Effects of Ultrasound

Many investigations have been carried out on changes in biological systems brought about by exposure to ultrasound. Some are basic studies into the general principles involved. Others are directed to therapeutic applications, and still others are concerned with possibilities for adverse effects associated with diagnostic procedures.

The nature and extent of biological changes produced by ultrasound

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A publication of The Hastings Center, 255 Elm Road, Briarcliff Manor, NY 10510 © 1987

depend on many variables. Results of experiments done on living small laboratory rodents (mice, rats, etc.) are quite different from those of experiments done on cell suspensions contained in test tubes or other vessels. In rodents, findings include hind limb paralysis (in neonatal mice), weight reduction (in mice exposed *in utero*) and accelerated repair of wounds (in perforated rabbit ears). In cell suspensions the findings have included change in transport of ions across cell membranes (rat thymocytes), change in surface electrical charge (Ehrlich ascites cells), increased tendency to clump (human platelets), altered rate of proliferation (HeLa cells) and lysis (various cells).

In the *in vivo* animal studies temperature elevation produced by the ultrasound is responsible for many, but not all, of the changes observed. By contrast, temperature elevation can usually be ruled out as an important factor in the *in vitro* experiments using cell suspensions; instead, the mechanism has commonly been shown, or assumed, to be some form of acoustic *cavitation*. The latter is a phenomenon of many complicated aspects, all of which must be considered in experiments with ultrasound, but not other radiations. As the term is used here, "cavitation" involves activity of small bodies of gas, dispersed in a suitable medium, when exposed to ultrasound. Aqueous media used in experiments with cell suspensions almost always contain microscopic gas bodies; these become sites of significant action when ultrasound is applied, under some conditions. Acoustic cavitation can affect cells by relatively gentle mechanical perturbation, by indirect chemical action through free radicals produced, or by violent mechanical disruption. While cavitation has mostly been observed in liquids, it also occurs in organized tissues, especially plants (whose intercellular spaces are filled with gas) and insects (whose respiration depends on gas-filled channels). It is not clear how the results for plants and insects should apply to mammals, since for these the mechanisms for gas transport (respiratory and circulatory systems) are very different.

Deleterious consequences of cavitation have been identified in laboratory animals exposed to ultrasound in some investigations; however, the experimental conditions differed significantly from those typical of ordinary medical practice. There is serious need for basic research to determine whether cavitation of any kind occurs in mammals under conditions used in diagnostic medicine or in routine physical therapy.

Table 1
Definitions

Acoustic Frequency: Number of cycles per second
Units
hertz (Hz): one cycle per second
kilohertz (kHz): 1000 Hz
megahertz (MHz): 1000 kHz

Upper limit of hearing for average person is 20 kHz.

In medical applications the frequency is usually in the range 1 to 10 MHz.

Acoustic pressure: Deviation (in a sound field) of the pressure from its original value.
Units
pascal (Pa)
megapascal (MPa): 1,000,000 Pa

A pressure of one megapascal is approximately equal to 7600 mm Hg, which is ten times standard atmospheric pressure. A deep sea diver at a depth of 320 ft is subjected to an increased pressure of 1 MPa.

Temporal peak pressure: Greatest value of acoustic pressure during a cycle.

Acoustic power of ultrasound source: Acoustic energy produced by the source per second.
Units
watt (W)
milliwatt (mW): 0.001 W

A typical adult human being produces heat through metabolism at an average rate somewhat greater than one watt (0.24 calories per second) per kilogram of tissue.

Acoustic intensity: Acoustic energy transmitted across unit area per second.
Units
watts per square centimeter (W/cm^2)
watts per square meter (W/m^2)
milliwatts per square centimeter (mW/cm^2)
$1\ W/cm^2 = 10{,}000\ W/m^2$
$1\ mW/cm^2 = 10\ W/m^2$

In a travelling plane wave of ultrasound (a situation often approximated in practice) an intensity of one watt per square centimeter is approximately equivalent to a temporal peak pressure of 0.17 MPa.

Spatial-peak temporal-average (SPTA) intensity (for a focused beam): Intensity at the focus, averaged over time.

Spatial-peak pulse-average (SPPA) intensity (for a focused and pulsed beam): Intensity at the focus, averaged over the duration of a pulse.

Acoustic Parameters

Whether a biological cell, tissue, or organism is affected by an application of ultrasound depends not only on the biological system, but also on physical characteristics of the ultrasound. Frequency is only one of the important parameters. Others of equal or greater significance are parameters indicative of the ultrasonic "level." A basic quantity for this purpose is the *acoustic pressure*, defined for any location and time as the deviation of the pressure produced by sound, at that location and time, from the original (atmospheric) pressure. As the wave passes a point of interest the acoustic pressure at that point takes on a range of positive and negative values; the largest of these values during a cycle (for continuous wave ultrasound) or during a pulse (for pulsed ultrasound) is called, for present purposes, the *temporal peak pressure* and is a possible quantity for characterizing the ultrasound "level" at the point in question.

In an application of therapeutic or diagnostic ultrasound the procedure is carried out by bringing a source of ultrasound, the *transducer*, into contact with the patient in some suitable way. The ultrasound field produced in the body of the patient is not uniform but, instead, the temporal peak pressure varies from point to point. In a focused field relatively large values occur in the focal region.

While acoustic pressure is a suitable quantity for characterizing an ultrasound field, the present U.S. standards on this subject are expressed mostly in terms of another quantity, the *acoustic intensity*. An ultrasound field possesses acoustic energy, which tends to flow outward from the source. The acoustic intensity at a point gives the rate at which acoustic energy crosses unit area of an imaginary surface, the latter being perpendicular to the flow at the point in question. Under many, but not all, conditions the intensity is proportional to the square of the acoustic pressure.

Unfocused fields, generated by devices used for therapy, are generally characterized by specifying the time-averaged intensity, spatially averaged over the transducer area.

A focused ultrasound field produced by a diagnostic device is usually characterized by specifying the intensity at the spatial peak, which occurs in the focal region. Two measures of the spatial peak intensity are given; one is averaged over the duration of a single pulse (typically only a few microseconds) and is called the *spatial-peak pulse-average (SPPA) intensity*. The other is averaged over all time, including the rather long intervals between pulses; this is the *spatial-peak temporal-average (SPTA) intensity*.

In addition to these intensities, the *acoustic power* is often used to characterize an ultrasound source. The acoustic power of a source is the total rate at which acoustic energy is transmitted from the source into the medium.

Table 2 shows ranges of values for these quantities that apply to commercial equipment used in medical ultrasound; those for therapy equipment are from References 2 and 6, while those for pulse-echo and Doppler equipment are from References 7 and 12. Values for the power generated by therapy units are higher than those for diagnostic units. The ranges for Doppler units extend to higher limits of power and intensity than those for pulse-echo devices. Also, SPTA (spatial-peak temporal-average) intensities for Doppler and, to a lesser extent, pulse-echo equipment extend into the range for average intensities applicable to therapy. However, the Doppler intensities apply only in a small focal region, while the therapy intensities apply over the cross section of a beam whose area is typically a hundred times larger than that of a focal region. The differences in biological effects between exposures of small focal regions and exposures of much larger regions have not been well defined.

The intensities characteristic of therapeutic ultrasound can be, and often are, high enough (deliberately) to produce a modest amount of temperature elevation. For diagnostic equipment the temperature rise produced is often very small and of little consequence. However, some degree of overheating might result if, in the course of a research investigation, the exposure parameters were to exceed those used in normal practice. For example, excess heating might occur if a beam of relatively high SPTA intensity were employed and/or if it remained focused on a given region of tissue for an extended period of time.

Similarly, there is no evidence of significant cavitation effects produced in the body under conditions indicated in Table 2 as typical of diagnostic ultrasound. However, it is possible that harmful cavitation would occur if the intensity or peak acoustic pressure were to exceed values normally used.

Statements and Recommendations from Professional Groups

The range of values given in Table 2 may be compared with information available on intensity levels at which biological effects have been observed. In experiments with laboratory mammals *in vivo* a variety of endpoints have been investigated. Positive results have been observed for a range of intensities and exposure times. Based on these studies, it has been possible to arrive at a generalization applicable to all such results which have been independently confirmed. This generalization, expressed in the form of a Statement, was approved by the American Institute of Ultrasound (AIUM). This and other Statements of the AIUM are presented and discussed in Reference 10. (See box for the "mammalian *in vivo*" Statement on page 4.)

A number of *caveats* were published along with this Statement, including the following:

- Most of the data apply to mammals

Table 2
Acoustic Power and Intensities

Given below are ranges of acoustical quantities characteristic of commercial ultrasound equipment used for physical therapy, as well as equipment for pulse-echo and Doppler techniques in diagnostic medicine. Data for therapy equipment are from References 2 and 6; note that the power and intensities are, in terms of watts (W). The SATA intensity given below (for therapy equipment) is averaged over time and is also averaged spatially over the face of the transducer. Data for diagnostic equipment are from References 7 and 12; the power (expressed here in terms of milliwatts (mW)) is typically much less than for therapy equipment. For diagnostic equipment the SPPA intensity (given here in W/cm²) can be a thousand times greater than the SPTA intensity (given here in mW/cm²). The peak acoustic pressures are calculated from rated values of the intensity; the highest values occur during the short pulses of Doppler or pulse-echo ultrasound. NA: Not Applicable

	Therapy	Pulse-Echo	Doppler
Power	0.5 - 20 W	0.01 - 75 mW	4 - 250 mW
Intensity (SATA)	0.1 - 3 W/cm²	NA	NA
Intensity (SPTA)	0.1 - 9 W/cm²	0.02 - 330 mW/cm²	65 - 1950 mW/cm²
Intensity (SPPA)	NA	2 - 300 W/cm²	30 - 1300 W/cm²
Pressure (Peak)	0.055 - 0.52 MPa	0.25 - 3.0 MPa	0.95 - 6.3 MPa

Statement on Mammalian In-Vivo Ultrasonic Biological Effects
August 1976
Revised October 1978; Reaffirmed October 1982

In the low megahertz frequency range there have been (as of this date) no independently confirmed significant biological effects in mammalian tissues exposed to intensities* below 100 mW/cm². Furthermore, for ultrasonic exposure times** less than 500 seconds and greater than one second, such effects have not been demonstrated even at higher intensities, when the product of intensity* and exposure time** is less than 50 joules/cm².

*Spacial peak temporal average as measured in a free field in water.
**Total time; this includes off time as well as on time for a repeated-pulse regime.

other than man, and it is not clear how to relate them to the human situation.

- Most experiments have not been repeated by independent investigators. Little research has been done with repeated short pulses such as would be most relevant to diagnostic ultrasound.
- The Statement carries a date and the committee is aware that exceptions might be found in future experiments.
- The Statement applied to data for mammals only and does not pertain to plants or to *in vitro* experiments.
- The Statement does not, in itself, imply specific advice on "safe levels" which might be universally valid. Determination of recommended maximum levels will require consideration of such difficult topics as: adequacy of present knowledge of biological effects; expected reliability of equipment specifications; assessment of patient benefits; and others. So far these matters have not been treated systematically.

Although the above Statement and accompanying warnings were first published in 1976, they are still widely accepted.

The intensity referred to in the above Statement is the SPTA intensity defined above and in Table 1. Also, according to Table 2, the SPTA levels generated by commercial diagnostic equipment extend beyond the 100 mW/cm² level. However, considering typical exposure times during diagnostic examinations, the intensity-time product may well be less than the 50 J/cm² value cited.

Furthermore, the SPTA values in Table 2 apply only very locally in the vicinity of a focus, while the experiments on which the Statement is based were done primarily with wider beams applied to mice and other small animals.

There is considerable reason for confidence in the safety of therapeutic and diagnostic ultrasound as usually practiced. While epidemiological surveys have not been carried out for therapeutic applications, the safety record is good. There are contraindications for its use, however, and users should be acquainted with recommended procedures. For example, the applicator should be moved constantly during treatment, to avoid localized overheating as well as other effects associated with nonuniformity in the tissue or in the acoustic field.[7,9,15,16] The National Council of Radiation Protection and Measurements (NCRP)[7] states, in respect to therapeutic ultrasound:

> There seems to be no recorded instance of significant harm to a patient attributable to an ultrasound treatment when applied according to recommended practice.

Several epidemiological surveys have dealt with diagnostic ultrasound, but have not found convincing evidence of any effects. After evaluating available results, the NCRP[7] concluded:

> There is no firm evidence that any physiological change, beneficial or not, is produced in patients by exposure to ultrasound during a diagnostic examination.

Consistent with the above conclusion is the statement on Clinical Safety arrived at by the AIUM.[10] (See bottom of page.)[10]

What about volunteers who are exposed to diagnostic ultrasound during the course of a research project? The last sentence of the Cinical Safety Statement would typically not apply to them; if the expected personal medical benefits are zero, they can hardly outweigh the risks, since the latter must be assumed nonzero, even though they are small.

This question has been given serious consideration by members of the medical community. A statement dealing with this topic, approved recently by the AIUM,[14] appears in the box on the next page.

Concerns of IRBs

In the "Safety Statement for Training and Research" the last sentence, in particular, should be considered by Institutional Review Boards (IRBs) when reviewing research proposals in which volunteers are to be exposed to diagnostic ultrasound. While "exposure conditions" are not defined in the Statement, they would clearly include the number and duration of exposures,[1] as well as acoustical data of the kind listed in Table 2.

To comply with the AIUM recommendation, investigators planning research need to carefully consider the exposures volunteers will receive in the proposed research. If commercial ultrasound equipment is to be used, information on the acoustic power and intensities should be supplied by the

AIUM Statement on Clinical Safety
October 1982
Revised 1983

Diagnostic ultrasound has been in use for over twenty-five years. Given its known benefits and recognized efficacy for medical diagnosis, including use during human pregnancy, the American Institute of Ultrasound in Medicine herein addresses the clinical safety of such use:

> No confirmed biological effects on patients or instrument operators caused by exposure at intensities typical of present diagnostic ultrasound instruments have ever been reported. Although the possibility exists that such biological effects may be identified in the future, current data indicate that the benefits to patients of the prudent use of diagnostic ultrasound outweigh the risks, if any, that may be present.

manufacturer. A widely accepted standard[11] stipulates that the acoustical data should, at least, be provided in the operator's manuals. It is recommended by many groups[2,6,7,10,13] that these data should be made available to users. The AIUM, through its Commendation procedure, publishes acoustical specifications, as well as other information, for manufacturers who voluntarily make the information available.[12]

It would be consistent with the AIUM Safety Statement for Training and Research to establish a requirement for proposals on research in which human volunteers would receive exposure to diagnostic ultrasound: In such a proposal information should be included on relevant acoustical parameters, and also on the number and duration of exposures planned. The proposal should also explain what will be done to see that, as recommended in the above Statement, volunteers are "informed of the anticipated exposure conditions, and of how these compare with conditions for normal diagnostic practice."

The AIUM Statement does not offer specific advice on how the volunteers are to be informed. The best means for doing this depend on the circumstances. Some individuals, as volunteers, would benefit from detailed technical specifications but most would probably need to have technical material explained to them. The following might be indicative of a satisfactory approach to informing volunteers about exposure conditions:

> If you agree to take part as a volunteer in this research you will receive a five-minute exposure to diagnostic ultrasound twice weekly for ten weeks. During each exposure an ultrasound transducer will be applied to your body in the same way as is done routinely to patients for purposes of --------. However, the patient would typically receive only three or four five-minute exposures, while you will receive a total of twenty.
>
> The equipment to be used is manufactured by X, Inc., as Model No. yyy, with which we plan to use transducer A215. For this ultrasound system the acoustic specifications are listed below. --------. These are exactly the same specifications as apply when the equipment is used to examine patients.

It should be understood that the above is given here only as an example, and applies only to that part of the consent form pertaining to the ultrasound exposure. For each proposal the facts to present may be different. Also, there are many possible choices of language for conveying the required information.

Safety Statement for Training and Research
October 1985

Diagnostic ultrasound has been in use for over 25 years. No confirmed adverse biological effects on patients resulting from this usage have ever been reported. Although no hazard has been identified that would preclude the prudent and conservative use of diagnostic ultrasound in education and research, experience from normal diagnostic practice may or may not be relevant to extended exposure times and altered exposure conditions. It is therefore considered appropriate to make the following recommendations:

> In those special situations in which examinations are to be carried out for purposes other than direct medical benefit to the individual being examined, the subject should be informed of the anticipated exposure conditions, and of how these compare with conditions for normal diagnostic practice.

For some situations the research investigators might decide that it is not useful to include quantitative acoustical data (such as that in Table 2) in the consent form. Omitting these data, or giving only selected data, may be appropriate if the information provided in the consent form is sufficient for making the recommended comparison, i.e., if the information is sufficient for comparing exposures the volunteer will receive to those which would be received by a patient in normal practice. However, even if the consent form does not contain quantitative acoustic data, *the research proposal itself should include this information.* Enough should be included, and discussed, to satisfy IRB members that the investigators are themselves knowledgeable about this aspect of the research.

ACKNOWLEDGMENTS

The author is grateful to a number of knowledgeable and concerned individuals for reading a draft of this paper and offering thoughtful comments. These include E. L. Carstensen (University of Rochester), N. L. Danigelis (University of Vermont), D. R. Gross (Texas A & M University), F. W. Kremkau (Bowman Gray School of Medicine), R. J. Levine (Yale University), R. A. Meyer (Children's Hospital, Cincinnati), J. A. Rooney (SpectroSonex), K. J. W. Taylor (Yale University) and M. C. Ziskin (Temple University). Special thanks are owed to Drs. Gross, Levine, Meyer, and Ziskin for their specific and valuable suggestions.

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